Appl. No.: 10/076,727
Amdt. Dated: 5/26/2005
Off. Act. Dated: 2/3/2005

REMARKS/ARGUMENTS

1. Introduction

Applicant has carefully considered all of the Examiner's comments. Claims 1-6 and 21-24 have been withdrawn as subject to a traversed restriction requirement as previously stated. Claims 7-20 are pending. Applicant responds below.

2. Restriction Requirement and Species Election – 35 U.S.C. § 121

Applicant notes that the restriction has been made FINAL. Notwithstanding such finality, it is further noted that the Examiner's reasoning is as follows:

> This [Applicant's arguments] are not found persuasive because the specification as filed discloses that the product of Group I may be used to culture cells. (Office Action page 2, 3rd paragraph)

MPEP Section 803 "Restriction – When Proper" states:

> Under the statute an application may properly be required to be restricted to one of two or more **claimed inventions** only if they are able to support separate patents and they are either independent. (emphasis added)

Applicant continues to traverse the restriction between Groups I and II based on the Examiner's reasoning that the invention "may be used to culture cell" (Office Action page 2, 3rd paragraph). Applicant has at no point **made claims** in the Group I apparatus claims 1-6 relating to the culture of cells. As such, Applicant continues to traverse the restriction as between Groups I and II, and respectfully requests reconsideration. Restating this, since restriction is only proper between two or more **claimed** inventions, and since cell culture was not **claimed** in Group I, then a restriction based only upon speculative uses not claimed should not be proper.

Should the Examiner find that Groups I and II are not subject to restriction based on the claimed invention, it is requested that withdrawn claims 1-6 be reinstated, and that the finality of the restriction be rescinded.

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3. Claim Rejections – 35 U.S.C. § 112

Claims 7, 13, and 15-20 stand "rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

Referring now to claim 7, the Examiner appears to state that it is unclear whether it is the three elements (of membrane corrals, membrane lipids and positively or negatively charged lipids) separately, or in a defined relationship, define a micro-array. (Office Action page 4 first paragraph)

Applicant believes such structural relationship is clearly set forth in the Applicant's specification, paragraph 66, which states:

> [0066] Referring now to Fig. 1, a micro-array device 100 is shown comprising four separate corrals 190. In each corral 190, a lipid bilayer 110 has been formed. The lipid bilayer 110 forms a continuous membrane within the corral 190. Each corral 190 is defined by a barrier material 180 that surrounds the corral and by a surface 120, which is either the same as or is formed upon a substrate 130. The barrier material 180 comprises an inner surface 185 (Fig 1A) in contact with the lipid bilayer 110 and also forms a physical separation between adjacent corrals 190 and prevents mixing of membrane components between adjacent corrals.

Thus, it appears from the specification that a micro-array is comprised of corrals, each of which has a lipid bilayer, with each corral defined by a barrier material. From the last sentence of the abstract:

> The lipid bilayer membranes are doped with various lipids and/or proteins to modulate the adherence of the cells being used in the device.

It is believed that the specification does contain sufficient disclosure that clearly sets forth the meaning of the term micro-array from the reasoning given above.

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Refer now to claim 13. The Examiner state that it is unclear whether the limitation "the lipid" of claim 13 refers to the "lipid bilayer membranes" of claim, or the "negatively or positively charged lipids" of claim 9. Claim 13 has been amended to clarify the limitation to "the dopant lipid".

Refer now to claims 13, 15, and 16, which were cited by the Examiner as having unclear antecedent basis. Although Applicant is not of the same opinion regarding the antecedent basis issue, in order to move past these issue claims 13 and 16 were modified to use the same "membrane composition elements" as used in unmodified claim 15.

With these amendments and remarks, it is now requested that the Examiner please reconsider all of the rejections above based on 35 U.S.C. 112.

4. Claim Rejections – 35 U.S.C. § 102(e)

4.1 Claims 7-20 stand "rejected under 35 U.S.C. 102(e) as being anticipated by Kam et al., U.S. publication number 2002/0009807." Applicant respectfully traverses these rejections as argued below, and requests reconsideration.

For a claim to be rejected under 35 U.S.C. 102(e) as being anticipated, each element and limitation must be taught.

In Kam, a method is taught of "**adhering cells to the cell adhesion compatible material such that the cells adhere only to the cell adhesion compatible material and not to the lipid bilayer expanse**" (Kam, paragraph 31, last sentence), which is exactly the opposite of Applicant's invention that instead teaches "[t]he lipid bilayer membranes are doped with various lipids and/or proteins to modulate the adherence of the cells being used in the device" (Applicant's Abstract, last sentence). Thus, Applicant teaches selective adhesion to lipid bilayers, while Kam teaches no adhesion to the lipid bilayer (Kam's "lipid bilayer expanse").

Additionally, in Kam's disclosure above, it appears that cells could only adhere to the barrier materials used to construct the device, e.g. fibronectin. Since Kam only

teaches cell adhesion to the fibronectin deposited on the substrate, in this sense the only cell adhesion occurs to the substrate, and not to the lipid bilayer expanse above it.

With the Kam reference now in mind, the detailed rejections are now addressed.

Referring now to claim 7, Kam fails to teach the limitation of: "a cell suspension with a micro-array comprising an array of adjacent membrane corrals, membrane lipids and positively or negatively charged lipids". Kam appears to concentrate on the use of fibronectin as applied as a barrier material to selectively adhere cells. As Applicant fails to include such a limitation, Kam cannot successfully be a 35 U.S.C. 102(e) reference for this claim 7. Applicant traverses the rejection and kindly requests reconsideration.

Referring now to Applicant's claim 8, the following limitation is seen:

c. determining the adhesion of the cells to the lipid bilayer membranes in different corrals in response to said different compositions.

As shown above, Kam fails to teach the determination of adhesion to the lipid bilayer membranes, and in fact Kam teaches directly away from such adhesion by instead stating cell adhesion to fibronectin. Therefore, Kam cannot be a successful 35 U.S.C. 102(e) reference. The Applicant therefore respectfully traverses the rejection and kindly requests reconsideration.

Dependent claims 9-13 depend from claim 8, which as argued above cannot be taught by Kam. Therefore, for the same reasons as above, Applicant respectfully traverses these rejections and kindly requests reconsideration of these claims as well.

Applicant's Claim 14 similarly contains the limitation of "observing cell adhesion to the membranes". For the same reasons as previously recited above, Kam fails to teach cell adhesion to membranes. Therefore, for the same reasons as above, Applicant respectfully traverses the rejection and kindly requests reconsideration of this claim.

Similarly, dependent claims 15-20 incorporate all of the limitations of base claim 14, and for the same reasons given above should also not be taught by Kam. Therefore, Applicant respectfully traverses these rejections and kindly requests reconsideration of these claims.

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4.2 Claims 7, 8, 14, 15, and 16 stand "rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. U.S. publication number 2002/0182633." Applicant respectfully traverses these rejections as argued below, and requests reconsideration.

Chen teaches several methods of selectively binding cells to substrates, but in the regime of lipid bilayers, only teaches a single instance of "PEO lipid bilayers" in their paragraph [0102]. PEO lipid bilayers are specially modified poly(ethylene oxide) lipid bilayers. These PEO lipid bilayers are not claimed in Applicant's application.

Conversely, Applicant's lipid bilayers floating within corrals are not described by Chen et al. Instead, Chen et al. generally appears to bind selectively only directly to substrates, and not to any lipid bilayers. Additionally, the PEO lipid bilayers appear, from what one may infer of the document, to be placed directly on the substrate. In this sense, they are yet another binding agent for the substrate, and have little of the cell-wall mimicking characteristics of Applicant's invention. For instance:

> "Fig. 4A schematically depicts direct photolithographically patterning of glass substrates with an extracellular matrix protein (collagen I) that is adhesive for many cell types..." (Chen et al. at paragraph [0103])

We now look to the individual independent claims, referring specifically to the issue of Applicant's lipid bilayer membrane, which is underlined as it occurs. Chen et al. fails to teach claim 7's limitation of:

> "a. contacting a cell suspension with a micro-array comprising an array of adjacent membrane corrals, membrane lipids and positively or negatively charged lipids" (Applicant's claim 7)

Likewise, Chen et al. fails to teach claim 8's limitation of:

> "a. providing a micro-array device having a plurality of lipid bilayer membranes disposed on a solid substrate in corrals separated by a barrier material" (Applicant's claim 8)

Similarly, Chen et al. fails to teach claim 14's limitation of:

"a. providing a micro-array of membranes in corrals displayed on a solid substrate, wherein the corrals contain membranes comprised of different compositions membrane composition elements of lipids, proteins, and other membrane-associated molecules" (Applicant's claim 14)

As a 35 U.S.C. 102(e) must teach all elements and limitations of a claimed invention in order to be a proper reference, it is submitted that Chen et al. fails in this regard. Applicant therefore respectfully traverses the Chen et al. rejections, and kindly requests reconsideration.

5. Claim Rejections – 35 U.S.C. § 103(a)

5.1 General remarks on obviousness under 35 U.S.C. 103(a).

"To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, to modify the reference or to combine reference teachings as discussed in subsection 3 (b) MPEP 2143.03. Additionally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985) MPEP 2142.

5.2 Claims 7-20 stand "rejected under 35 U.S.C. 103(a) as being anticipated by Chen et al., U.S. Publication number 2002/0182633 and Boxer et al., U.S. Patent number 6,228,326."

Applicant respectfully traverses the rejections, responds below, and requests reconsideration of the claims in question.

MPEP § 2143 requires that "[t]o establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of

ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations."

Chen et al. reference

As described above, Chen et al. teaches only the direct binding to a substrate, and fails to teach cell binding to lipid bilayers floating in corrals. As the Examiner correctly states: "The reference of Chen et al., does not disclose...the solid substrate is separated from the membranes by a water layer" (page 9, lines 3-5). Chen at best really only describes non-adhesion of cells to PEO lipid bilayers, as stated by Chen's paragraph [0103] excerpt reading "PEO polymers ... are non-adhesive for both proteins and cells."

Chen et al. does refer to the use of "novel substrates such as PEO lipid bilayers [59]" in paragraph [0102]. The PEO lipid bilayer reference [59] relates to a publication submitted with this response in an Information Disclosure Statement, which is: Dori, Y., H. Bianco-Peled, S. K. Satija, G. B. Fields, J. B. McCarthy, and M. Tirrell, "Ligand accessibility as means to control cell response to bioactive bilayer membranes," Journal of Biomedical Materials Research, 2000.50(1): p, 75-81.

In this paper by Dori et al., one finds only a single reference to PEO on page 78, column 2, in the paragraph beginning with "Figure 4..." The Dori et al. reference continues to elaborate:

> "In addition, Prime and Whitesides[32] showed that self-assembled monolayers (SAMs) of poly(ethylene oxide) (PEO) with only two EO segments have the ability to prevent protein adsorption."

Therefore, Chen et al. in fact misquotes the Dori et al. reference, which more likely should have been that monolayers of PEO "with only two EO segments have the ability to prevent protein adsorption." Thus, Chen cites a reference that never appears to discuss the term "PEO lipid bilayer".

Since Chen ultimately only refers to PEO monolayers, as shown above, Chen does not appear to make a "suggestion or motivation" to use Applicant's "lipid bilayers", and thus cannot be a useful 35 U.S.C. 103(a) reference. Second, Chen's PEO monolayers have only been shown to "prevent protein adsorption", and in that sense, either directly teaches away from Applicant's invention, or doesn't refer to adsorption of cells in any way. Third, Chen's PEO monolayers would appear to have to be directly deposited on the substrate, and would not be comparable to Applicant's micro-arrays of lipid bilayer membranes as one cannot deposit a lipid monolayer over a water layer, as such a deposit would be unstable, thus using Chen's teaching of PEO monolayers with the Boxer et al. patent would have no reasonable expectation of success. Fourth, Chen's prevention of cell adsorption directly teaches away from Applicant's claim 7.b limitation of "observing cell adhesion", and therefore would have no expectation of success.

Additionally, lipids directly attached to a substrate have a static nature, in that they cannot move, and are "locked" in place by the substrate. By contrast, lipid bilayers membranes over a water layer are free to move about and rearrange to minimal energy configurations, and hence are dynamic in nature. A rigidly static lipid, even if Chen et al. had taught it, would have only remote similarity to dynamic lipid bilayer membranes. Furthermore, the dynamic lipid bilayer membranes tend to much more closely model segments of intact cell walls, and thus would be more useful for cell-cell interaction studies.

For the reasons stated above, it would appear that Chen et al. would not suggest or motivate one to combine it with the Boxer et al. reference teaching patterned lipid bilayers over a water layer.

Boxer et al. reference

Boxer et al. fails to teach the binding of cells to a lipid bilayer. Boxer et al. does teach the use of lipid bilayer membranes over a water layer.

Regarding the dynamic nature of dynamic lipid bilayer membranes, Boxer et al. states at column 7, lines 1-5:

> "Functionally, the suitability of a material for use as a bilayer barrier surface region or a bilayer-compatible surface region may be evaluated by the material's performance in a simple "fluorescence recovery after photobleaching" (FRAP) test".

Boxer continues at column 7, lines 31-34, to state that:

> "When the above test is carried out using a material capable of forming a bilayer-compatible surface, vesicles in the suspension will have fused with the surface forming a supported bilayer containing the fluorescent reporter, and the localized exposure to photobleaching light will have bleached the area of the bilayer corresponding to the region of the surface on which the photobleaching light was focused. During the monitoring period, fluorescence in the bleached area of the bilayer will recover due to the fluidity of the supported bilayer."

Thus, Boxer et al. essentially states that a usable lipid bilayer membrane over a water layer will exhibit FRAP recovery. Any layer using the teachings of Chen et al. would fail to exhibit such FRAP recovery as the layer would be bound to the substrate and hence static.

As Chen et al. teaches of layers bound to the substrate, and Boxer et al. teaches a lipid bilayer supported by a water layer that has a fluid or dynamic nature, both references teach opposing techniques. The combination of both would work for neither, and there would be no reasonable expectation of success by such an unlikely combination.

Conclusion of Rejections of Claims under 35 U.S.C. 103(a).

The Applicant believes the Examiner has failed to establish a *prima facie* case of obviousness as set forth above for the various 35 U.S.C. 103(a) rejections addressed above. Applicant further believes that these grounds for rejection have been sufficiently addressed and overcome, and respectfully requests reconsideration and withdrawal of these grounds for rejection.

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6. Additional Claim Fees

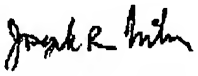
No claims have been added, therefore there is no additional claim fee.

7. Conclusion

In view of the above, Applicant has fully responded to the Office Action. Although the Group I and II restriction requirement has been made FINAL, Applicant respectfully requests reconsideration of the finality with respect to the claimed subject matter of Group I.

Date: May 26, 2005

Respectfully submitted,



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